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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/772,445	02/06/2004	Ravi Upasani	1483.0340003	5165

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EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/772,445	RAVI UPASANI	
	Examiner	Art Unit	
	CECILIA M. JAISLE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18 and 20-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *18 and 20-23* is/are allowed.

6)☒ Claim(s) *24-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06-04-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Restriction

Applicants' election of Group I, with traverse, claims 18 and 20-23, in the Response of Jun. 4, 2008, is acknowledged. Applicants assert that a search for all Groups together would not be burdensome. However, literature searches for each of the various Groups would not be coextensive. Additionally for all the reasons of record in the Office Action of Mar. 4, 2008, this restriction is deemed proper.

Claims 24-31, drawn to Group III, methods using Group I, are subject to rejoinder if elected claims 18 and 20-23, drawn to Group I, are found to be allowable. Claims drawn to compounds of Group II and methods of Group IV are not subject to rejoinder.

Rejoinder

Claims 18 and 20-23 are directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(b), claims 24-31, directed to the process of using the allowable product, previously withdrawn from consideration as a result of a restriction requirement of Mar. 4, 2008, are hereby rejoined and fully examined for patentability under 37 CFR 1.104. Claims directed to the inventions of Groups II and IV do not require all the limitations of an allowable product claim, and have NOT been rejoined.

Because a claimed invention previously withdrawn from consideration under 37 CFR 1.142 has been rejoined, **the restriction requirement between Groups I and III as set forth in the Office action mailed on Mar. 4, 2008 is hereby withdrawn**. In

view of the withdrawal of the restriction requirement as to the rejoined inventions, applicants are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01. Applicants may still file proper divisional applications directed to any of the inventions of Groups II or IV.

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not provide enablement of claims 24-31, especially where these claims contain such recitations as:

> ... treating, preventing or ameliorating neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery; or treating or ameliorating a neurodegenerative disease selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease and Down's syndrome; or treating, preventing or ameliorating the adverse consequences of the overstimulation of the excitatory amino acids; or treating, preventing or ameliorating anxiety, psychosis, convulsions, chronic pain, migraine headache, glaucoma, retinitis, urinary incontinence or inducing anesthesia; or enhancing learning and cognition; or treating or ameliorating schizophrenia and myoclonus...

The following reasons apply to this enablement rejection.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. The disclosure in this application is not sufficient to enable the instantly claimed methods based solely on the disclosed *in vitro* treatment of cancers of the specific types enumerated above and described in the specification (pages 48-52, *inter alia*).

MPEP § 2164.01(a) states:

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of

predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed.Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. **Breadth of the claims:**

(a) Scope of the compounds. Claims 24-31 cover potentially billions of compounds of varying scope of Group I. The compounds are quinazolinone derivatives with a particular substitution pattern and are of varying scope in the different method claims.

(b) Scope of the diseases covered. Claims 24-31 are directed to a method for

- treating, preventing or ameliorating neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia or surgery; or
- treating or ameliorating a neurodegenerative disease selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease and Down's syndrome; or
- treating, preventing or ameliorating the adverse consequences of the overstimulation of the excitatory amino acids; or

- treating, preventing or ameliorating anxiety, psychosis, convulsions, chronic pain, migraine headache, glaucoma, retinitis, urinary incontinence or inducing anesthesia; or
- enhancing learning and cognition; or
- treating or ameliorating schizophrenia and myoclonus,

in an animal, for which the disclosure is non-enabling.

To the extent that claims 24-31 recite "preventing" various conditions/diseases, the disclosure does not teach how to identify a host with the potential to develop such conditions/diseases or how to provide preventive measures to the identified host. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as pharmaceutical arts. The scope of prevention of the recited conditions/diseases is not enabled based on procedures provided in the specification. "Prevent" means *to keep from happening, preclude, to anticipate,* etc. (Webster's Comprehensive Dictionary, 1996). In addition, "preventing" includes prevention of all sequelae conditions caused by or associated with such conditions/diseases that are known to exist and that may be discovered in the future, for which no enablement is provided. The specification fails to teach one skilled in the art how to identify the host and therapeutic regimen for administration of the instant compounds to achieve the desired preventive effect. No evidence of record enables a skilled artisan to identify hosts with the potential to develop the recited conditions/diseases described herein.

The specification fails to specify the type of **stroke** intended and there are various types. A **stroke** may be caused by too little blood in the brain (ischemic stroke) or by too much blood within the skull (hemorrhagic stroke):

- Ischemic stroke: About 80 percent of strokes are ischemic. Blood clots or other particles block arteries to the brain and cause severely reduced blood flow (ischemia), depriving brain cells of oxygen and nutrients, leading to cell death. The most common ischemic strokes are:
  - Thrombotic stroke. Occurs when a thrombus forms in an artery, e.g., a carotid artery, supplying blood to the brain. A clot forms in areas damaged by atherosclerosis. Plaques that completely clog or markedly narrow an artery may also cause ischemic stroke.
  - Embolic stroke. Occurs when a blood clot or other embolus forms in a blood vessel away from the brain, e.g., the heart, and travels through the bloodstream to lodge in narrower brain arteries. This may be caused by atrial fibrillation.
- Hemorrhagic stroke. Occurs when a blood vessel in the brain leaks or ruptures, caused by uncontrolled high blood pressure (hypertension), weak spots in blood vessel walls (aneurysms), or, less commonly, rupture of an arteriovenous malformation (AVM), a malformed tangle of thin-walled blood vessels, present at birth. There are two types of hemorrhagic stroke:
  - Intracerebral hemorrhage. A blood vessel in the brain bursts and spills into the surrounding brain tissue, damaging brain cells and depriving them of blood. High blood pressure is the most common cause of hemorrhagic stroke.

- Subarachnoid hemorrhage. Bleeding starts in a large artery on or near the membrane surrounding the brain, often signaled by sudden, severe headache, commonly caused by rupture of an aneurysm. After subarachnoid hemorrhage, vessels may go into vasospasm, causing brain cell damage by further restricting or blocking blood flow to portions of the brain.

The specification fails to specify the type of **ischemia** intended and there are various types. **Cardiac ischemia** may cause chest pain, known as angina pectoris. **Bowel ischemia** is an ischemia in the large bowel caused by an inflammation that results in ischemic colitis. Ischemia in the small bowel, caused by inflammation, results in **mesenteric ischemia**. **Cutaneous ischemia** involves reduced blood flow to skin layers and may result in mottling or uneven, patchy skin discoloration. **Silent ischemia** is an ischemic episode without pain. In **myocardial ischemia**, oxygen deprivation to the heart muscle is accompanied by inadequate removal of metabolites because of reduced blood flow or perfusion.

Many theories have attempted to explain **Schizophrenia**. Currently, it is believed to result from a physiological condition brought out by a life stressor. Symptoms of Schizophrenia typically begin between adolescence and early adulthood for males and a few years later for females, usually as a result of a stressful period (such as beginning college or starting a first full time job). Initial symptoms may include delusions and hallucinations, disorganized behavior and/or speech. As the disorder progresses symptoms such as flattening or inappropriate affect may develop. Medication is the most important part of treatment as it can reduce and sometimes

eliminate psychotic symptoms. Case management is often needed to assist with daily living skills, financial matters and housing. Therapy can help the individual learn better coping skills and improve social and occupational skills. **There is no known prevention or cure for Schizophrenia** so prognosis is poor. However, medication has been shown to be quite effective against psychotic symptoms and therapy can help the individual cope with the illness better and improve social functioning. Absence of what is termed negative symptoms (flattened affect, avolition and poor social interaction) significantly improves prognosis.

The other diseases/conditions recited in the claims similarly cover a wide variety of conditions which are insufficiently enabled by the specification.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is physiological in nature. The invention is directed toward therapeutic use of the claimed compounds in treating/preventing/ameliorating all the recited diseases/conditions in claims 24-31.

Applicants do not provide highly predictive competent evidence or recognized tests to prevent, treat or ameliorate all diseases/conditions recited for the claimed compounds of varying scope of Group I. Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present,

> "The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."

Plant Genetic Systems v. DeKalb Genetics, 65 USPQ2d 1452 (CAFC 2003).

It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

3. **Direction and Guidance:** That provided in the specification is very limited. The dosage range information is meager at best. It is generic; the same for all diseases/condition claims 24-31 covers. No specific direction or guidance provides a regimen or dosage effective specifically for preventing, treating or ameliorating all of the diseases/conditions in "an animal."

4. **State of the prior art:** The state of the art indicates a need for undue experimentation. The present compounds of Group I are said to be antagonists of (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) ionotropic receptors. Certain of these compounds are said to be positive modulators of AMPA receptors.

Elting, et al., Stroke, Dec. 2002, 2813-2818, recognize the disappointing results of AMPA antagonist therapy in regard to stroke and ischemia:

> Several AMPA antagonists have been developed as neuron-protective compounds and have entered clinical development. None of these compounds has reached phase 3 clinical trials, and **unacceptable adverse events** can be the main obstacle. The most prominent finding of this study was that the administration of the AMPA antagonist ZK200775 in ischemic stroke patients resulted in a transient neurological deterioration, which was associated with a higher than expected rise in serum S-100B levels.

Bolton, et al., Mediators of Inflammation, Vol. 2006, Article ID 93684, pp. 1-12, emphasize the need for further research regarding AMPA antagonist therapy of CNS trauma: "... [C]ompounds designed to antagonize the agonist actions on NMDA and AMPA/kainite receptors administered either alone or in combination with other therapies **may** offer the real prospect of treatment for patients with MS and related disorders of the CNS."

Fumagalli, et al., Experimental Neurology, 198 (2006), 114-128, found:

> Chronic treatment with the AMPA antagonist RPR119990 is ineffective in improving motor impairment, in reducing **motoneuronal loss** and muscular atrophy in treated mice. ...
>
> Consistently, treatment of wobbler mice with the competitive AMPA antagonist RPR119990 did not show positive effects on the onset and the progression of the wobbler disease, as well as on motoneuron number and biceps atrophy.

Wobbler disease is a condition in dogs and horses of the cervical vertebrae that causes an unsteady (wobbly) gait and weakness.

Moloney, Nat. Prod. Rep., 2002, 19, 597-616, reported minimal understanding of the relationship between excitatory amino acids [EAA] and AMPA antagonists:

> EAA receptors (iGluR and mGluR) can be classified using sequence homology, pharmacological behaviour and their mechanisms of signal transduction, and they exist in several sub-types: the N-methyl-D-aspartate (NMDA) receptor has 6 sub-types (NR1, NR2A-2D and NR3A), the (S)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) receptor 4 subtypes (GluR1-4), the KA receptor five sub-types (GluR5-7, KA1, KA2) and the mGluRs have eight sub-types (mGluR1-8). One key goal yet to be satisfactorily resolved for many of them concerns the identification of fully selective agonists and antagonists for each receptor sub-type.

Bergink, et al., Eur. Neuropsychopharmacol. 14 (2004) 175-183, noted negative correlation between AMPA antagonists and anxiety and CNS therapy in general: "AMPA antagonists displayed anxiogenic actions in three studies with conditioned and unconditioned tests." Bergink cautioned: "However, in general the utility of NMDA and AMPA/kainite antagonists appeared to be greatly hampered by ad-verse effects because of interference with receptors throughout the whole CNS and body."

In a study of AMPA antagonist effects on activation of glutamate neurontrans-mission in the prefrontal cortex, Takahata, et al., Neuropsychopharm. (2003) 28, 1117-1124, expressed reservation about murine subjects as psychosis models: "...hyperlocomotion in the rodent **may** be a useful measure of limbic malfunction and the propensity of PCP [phencyclidine] to produce psychosis in man."

De Sarro, et al., Current Topics in Med. Chem. 2005, 5, 31-42, emphasized the need for combined agents in anti-convulsant therapy:

> Whereas selective inactivation of AMPA receptors can provide information of the therapeutic contribution of each receptor subtype alone and help to map epileptic circuitry in the brain, ultimately, antiepileptic drugs directed at the glutamatergic system are likely to be most beneficial when they involve a combination of agents including AMPA receptor modulators.

Sang, et al. Cephalagia, 2004, 24, 596-602 (Abstract) recommended further research on the use of LY293558, an AMPA/GluR5 antagonist, in migraine headache therapy: "The efficacy and safety results of LY293558 in this small migraine proof of concept trial, together with supportive preclinical data, provide

evidence for a potential role of nonvasoactive AMPA/KA antagonists in treating migraine. Larger trials are needed to further test the hypothesis."

Bigal, Headache Currents, Vol. 1, No. 1, Jul. 2004, 20-21 (Abstract), reports disappointing results for the AMPA antagonist LY300168 in migraine therapy: "The lack of efficacy of the selective AMPA antagonist LY300168 in PPE [dural plasma protein extravasation] does not support a role for this mechanism in migraine."

This information emphasizes the need for research in therapy of these diseases/conditions with AMPA antagonists, such as the present compounds.

5. **Working Examples:** The specification working examples do not show *in vivo* treatment of all recited diseases/conditions. The state of the art (e.g., Elting, Bolton, Fumagalli, Moloney, Bergink, Takahata, De Sarro, Sang, Bigal and) supports that successful prevention/treatment/amelioration of the diseases/conditions as recited by the claims is a subject for further investigation.

No examples show prevention/treatment/amelioration of diseases/conditions as the claims recite in "an animal." Testing described at p. 94 and reported in Table 1 fails to identify test conditions or specific animals in which electroshock convulsions were induced. Applicants do not provide highly predictive competent evidence or recognized tests. The compounds are disclosed to modulate AMPA receptors and the specification states that these compounds are therefore useful to prevent-treat-ameliorate diseases/conditions, as recited by claims 24-31, for which Applicants provide no competent *in vivo* evidence. Furthermore, Applicants do not provide

competent evidence that the instantly disclosed tests are highly predictive for all methods disclosed and embraced by the claim language for the intended host.

6. **Skill of those in the art:** The articles discussed above demonstrate that enablement was not established for the claimed methods as of the filing date.
7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, one skilled in pharmaceutical arts would have an undue burden to make and use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art indicates the requirement for undue experimentation. The ability of an agent that modulates AMPA receptors to prevent/treat/ameliorate the diseases/conditions recited by the claims remains open to further study and proof.

Consideration of the above factors demonstrates that the present application sufficiently lacks enablement of claims 24-31. In view of the breath of the claims, the varying scope of compounds in the various claims, the pharmaceutical nature of the invention, the unpredictability of relationship between AMPA receptor modulation and prevention/treatment/amelioration of the diseases/conditions recited by the claims, one of ordinary skill in this art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Allowed Claims

Claims 18 and 20-23 are allowed. Following is an examiner's statement of reasons for allowance. Claims 18 and 20-23 have been amended to avoid the rejection under 35 USC 102(b) over the Haider reference, as set forth in the Office Action of Mar. 4, 2008. Claims 18 and 20-23 are not anticipated or rendered obvious over Haider or any of the other prior art of record, whether taken individually or in any combination.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CECILIA M. JAISLE, J.D. whose telephone number is (571)272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

CECILIA M. JAISLE, J.D.

8/1/2008